METABOLIC AND HEMODYNAMIC ADJUSTMENTS TO HYPOXIA IN INFANCY*

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HYPOXIA is a term generally used to indicate a lack of adequate oxygen requirements for the normal metabolic functions of the body, whereas hypoxemia indicates a decrease in the normal oxygenation of arterial blood. It is important to realize that it is possible for an individual to have considerable hypoxemia without necessarily demonstrating tissue hypoxia. The limits to which arterial blood oxygenation may be lowered before tissue hypoxia becomes evident will depend on the oxygen requirements of the cells. The most obvious evidence of hypoxia in cells is the interference with the final degradation of lactic acid to carbon dioxide and water, so that lactic acid accumulates in greater than normal quantities and is liberated into the blood. Huckabee[1] has demonstrated in the adult animal that lactic acidosis usually develops when the oxygen tension (Po_2) in arterial blood drops below 35 to 40 mm.Hg. Little information has been available regarding the response of the neonate and infant to hypoxia or hypoxemia. The normal fetus in utero is exposed to an arterial Po_2 level of only about 30 mm.Hg, as indicated by measurements on umbilical arterial blood in the sheep and goat fetus.[2] At these levels of Po_2, the fetus does not become acidotic, since umbilical arterial *p*H is only minimally higher than that of the mother. It is clear that there must be some change in metabolic processes after birth, when the arterial blood Po_2 rises to about 100 mm. Hg, and any reduction to levels below 35 to 40 mm. Hg results in acidosis. The nature of these changes is as yet not clear. Severe acidosis is extremely common in infants subjected to prenatal or perinatal asphyxia, as has been shown by James,[3] but the levels to which fetal Po_2 must fall before acidosis develops have not been determined.

In infants with normal circulation, the persistence of certain fea-

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tures of the fetal circulation has an important influence on their response to hypoxia, and the presence of some congenital heart lesions may have similar effects.

Infants with cyanotic congenital heart lesions that produce severe arterial hypoxemia usually have anomalies that interfere with actual pulmonary blood flow, as in severe pulmonary stenosis, or with effective pulmonary blood flow, as in transposition of the great arteries. In this latter condition, although total pulmonary blood flow is not low, the amount of venous blood reaching the lungs for oxygenation may be markedly reduced. When oxygen availability is limited, these infants develop hypoxemia and respond in the usual manner by developing a lactic, or metabolic, acidosis. We have repeatedly demonstrated the presence of acidosis, often of extreme degrees, with *p*H levels below 7.0, in some of these infants, when arterial P_{O_2} was below 35 mm.Hg.

The usual response to a lowered *p*H is an increase in ventilation to attempt to exhale excess carbon dioxide (CO_2), thus lowering carbonic acid (H_2CO_3) levels, compensating for the rise of other organic acids. The chemoreceptor response to hypoxemia and the respiratory center response to acidosis occurs in these infants, as evidenced by the marked increase in ventilation. However, since pulmonary or effective pulmonary blood flow is markedly limited, carbon dioxide cannot be eliminated in quantities large enough to compensate for the metabolic acidosis. Thus, in spite of the usual increase in ventilation, there is a failure of the respiratory compensating mechanism due to inadequate perfusion and a severe uncompensated metabolic acidosis results. Whereas usually in metabolic acidosis, arterial blood carbon dioxide tension (P_{CO_2}) is lowered, in these infants with congenital heart disease, the arterial P_{CO_2} is usually near normal or sometimes even elevated. Figure 1 shows the results obtained during cardiac catheterization in four patients who had severe hypoxemia at the time of study. The effects of the hyperventilation with inadequate perfusion is well shown in the high P_{O_2} very low P_{CO_2} and normal or high *p*H in pulmonary venous blood. However, systemic arterial P_{O_2} is extremely low, and *p*H is reduced considerably.

Since there is a failure of respiratory compensation in these infants, acid-base regulation is now dependent mainly on renal mechanisms. Little is known, however, regarding kidney function in the presence of severe hypoxemia. Spears[4] has examined the kidneys of infants and

DATA ON FOUR CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE

Patient				Systemic Arterial					Pulmonary Venous					Flows (ml./min./m²)	
Initials	*Sex*	*Age*	*Diagnosis*	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	*pH*	HCO_3– (mEq./l.)	% Sat.	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	*pH*	HCO_3– (mEq./l.)	% Sat.	*Pulmonary*	*Systemic*
J.C.	M	4 yr	Tetralogy of Fallot	34	37	7.24	15.2	40.0	—	—	7.4	—	—	1,100	4,500
D.G.	F	6½ mo	Pulmonary atresia; ventricular septal defect; patent ductus arteriosus	21	36	7.05	9.8	22.0	100	18	7.4	10.8	96.6	1,500	5,000
G.C.	M	5 mo	Transposition of the great vessels with patent foramen ovale	24	36	7.20	13.6	25.0	93	27	7.4	15.8	97.4	800*	4,400
E.S.	M	5 da	Severe pulmonary stenosis with patent foramen ovale	37	34	7.28	15.2	48.5	98	26	7.4	15.3	100	750	1,950

*Effective pulmonary flow.

Fig. 1

children who have died after long periods of chronic hypoxemia due to congenital heart disease. He described definite glomerular changes, but the tubules were only mildly affected. In spite of the lack of histological changes in the tubules, it is quite possible that there is an interference with tubular function, particularly since the tubules are metabolically so very active. We have performed studies of acid secretion and alkalinizing mechanisms in the kidney in one infant during episodes of hypoxemia. There was a decrease in acid secretion and a mild acidosis, which became more marked during the period of hypoxemia.

Hypoxemia and acidosis produce significant interference with cardiovascular function. Darby[5] demonstrated that when *p*H drops below 7.1, blood pressure falls, due to a decrease in myocardial contractility, and he also described a decrease in myocardial inotropic response to catecholamine infusion. The effects on myocardial function have been more intensively studied by Downing *et al.*,[6] who showed in studies in newborn lambs that hypoxemia alone, in the presence of normal *p*H, produced little depression of myocardial function. A reduction of *p*H in normal P_{O_2} environment caused some decrease in contractility, but a combination of hypoxemia and acidosis caused a profound reduction in myocardial contractility.

In addition to these general effects on the circulation, the newborn animal and infant are particularly susceptible to the effects of hypoxia and acidosis by virtue of their reactive pulmonary vasculature. In the adult the small pulmonary blood vessels have thin walls and large lumina, and they respond to hypoxia with mild constriction. The fetal and neonatal pulmonary vessels have thick muscular media, and these vessels are extremely responsive to changes in oxygen environment.[7, 8] Although it has been accepted that hypoxia is a potent vasoconstrictor of the pulmonary vessels, there has been little information regarding the levels of hypoxia that cause constriction, or of the magnitude of the response with different degrees of hypoxia.

We studied the responses of the pulmonary circulation in newborn calves, in which pulmonary blood flow was directly measured by means of an electromagnetic flow probe on the main pulmonary artery after ligating the ductus arteriosus.[9] Pulmonary venous and systemic arterial P_{O_2} was modified by ventilating the animals with various gas mixtures of oxygen in nitrogen. These studies showed that reduction of P_{O_2} had little effect on pulmonary vascular resistance until it fell to levels below

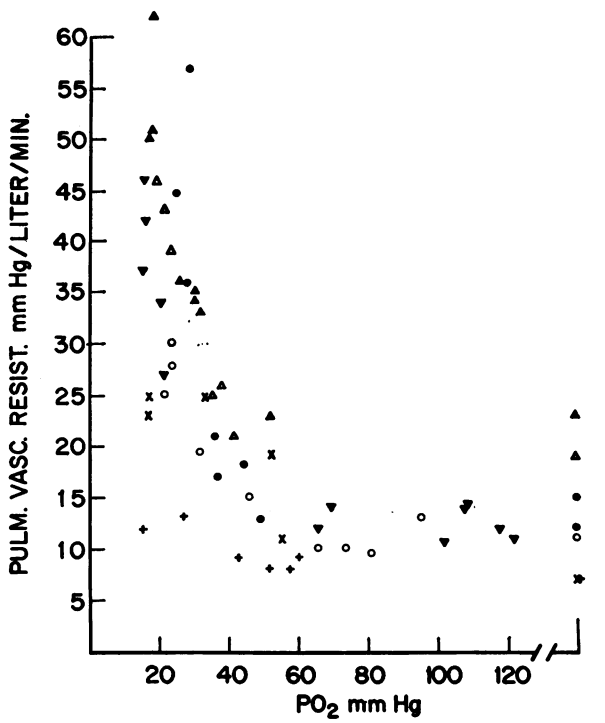

Fig. 2

45 to 50 mm. Hg, when there was a slight rise. Further reduction of P_{O_2} resulted in very marked increases in pulmonary vascular resistance, with extreme responses to very small changes of P_{O_2} in the P_{O_2} range of 20 to 30 mm. Hg (Figure 2).

Considerable individual variation in the hypoxic response to hypoxia was noted and, although part of this could be explained on the basis of age (the older calves showing less response), there was also a striking association with *p*H changes. Enson *et al.*[10] have described a dependence of hypoxic response of the pulmonary circulation on *p*H levels. We were able to document conclusively the very striking interrelationship between pulmonary vascular resistance, *p*H, on P_{O_2}. This is well shown in Figure 3, which gives the response in one animal. When arterial *p*H was above 7.3, a reduction of arterial P_{O_2} from levels above 100 mm. Hg to 20 mm. Hg produced only a small change in pulmonary vascular resistance. However, when *p*H is decreased further, a marked increase in pulmonary vascular resistance occurs with decrease of P_{O_2} from 100 to 20 mm. Hg. By combining the results of all the experiments the relationship between pulmonary vascular resistance, P_{O_2} and *p*H is

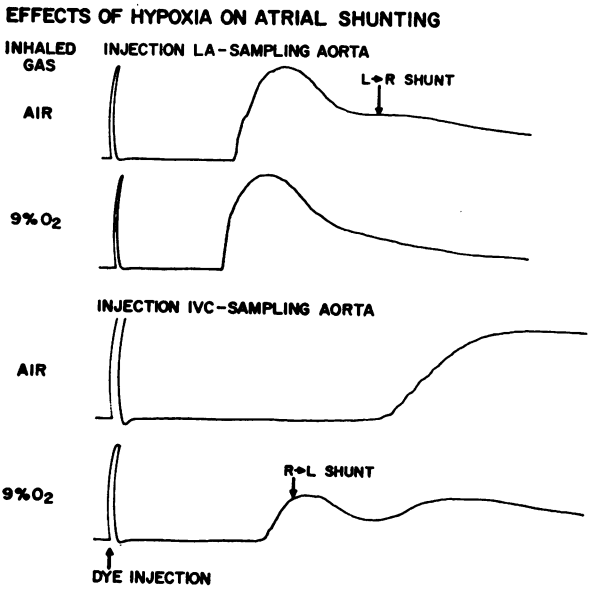

Fig. 3

diagrammatically represented in Figure 4.

Since the neonatal circulation is still in a stage of transition, and since the ductus arteriosus and foramen ovale are not permanently sealed, a change in pulmonary vascular resistance produced by hypoxia and acidosis may produce marked alterations in the hemodynamics of the circulation. Indicator-dilution studies performed in the calves showed that while breathing air no significant foramen ovale shunting could be demonstrated, but that when hypoxia and acidosis were induced, enormous right-to-left shunts through the foramen ovale developed, as shown in Figure 5.

This phenomenon, peculiar to the newborn animal and infant, would tend to accentuate the hypoxemia by direct passage of venous blood into the arterial circulation. Furthermore the profound effect of hypoxia and acidosis on the pulmonary vasculature would tend to increase pulmonary blood flow, thus interfering with respiratory compensation by elimination of CO_2 and thus accentuating the acidosis. The effect is similar to that in the infant with congenital heart disease and decreased pulmonary blood flow.

A vicious cycle is thus established, whereby increasing hypoxia and acidosis cause pulmonary vasoconstriction, decreasing pulmonary blood flow, causing CO_2 accumulation, accentuating the acidosis. The

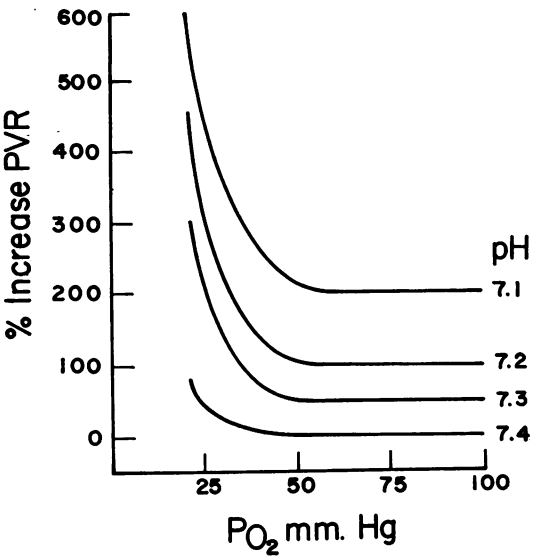

Fig. 4

possible importance of this mechanism in infants with the respiratory distress syndrome has been stressed by Chu *et al.*[11]

This effect of hypoxemia on the pulmonary circulation may also be important in the fetus in utero, where it may play an important role in distribution of the fetal circulation. Preliminary studies we have performed in the fetal lamb or kid in utero indicate that apparently small changes in fetal P_{O_2} may have a marked influence on pulmonary flow.

Similar responses may occur in the infant with chronic respiratory disease with no cardiac problems, as demonstrated by hemodynamic observations in an infant with a history of repeated infection since birth who developed an acute lower left lobe atelectasis. Cardiac catheterization at this time showed pulmonary arterial hypertension with severe hypoxia (Table). The infant developed marked cardiomegaly with some right heart failure; after the pulmonary problem had been relieved, he reverted to a normal hemodynamic status and heart size diminished rapidly.

The appreciation of the dramatic effects of acidosis secondary to severe hypoxemia is extremely important in treating infants with this condition. It should be realized that oxygen administration is often not very helpful in these patients, particularly in those with congenital heart disease. The marked limitation in pulmonary blood flow does not

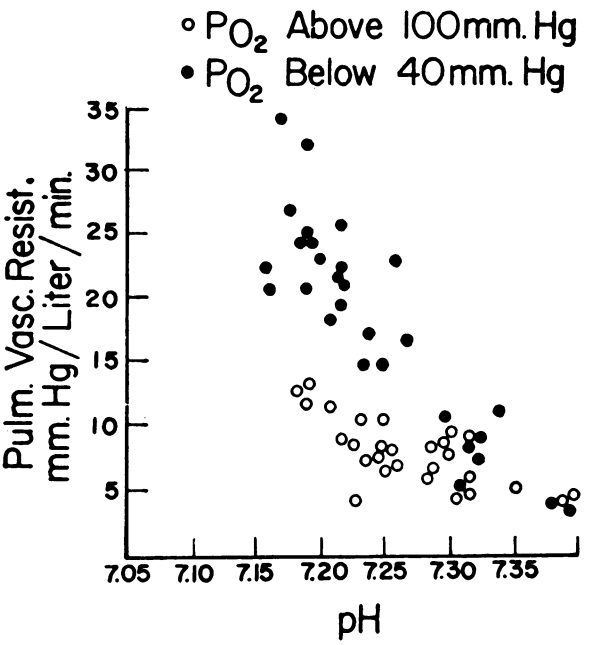

Fig. 5

HEMODYNAMIC STUDIES IN INFANT G.L.

RECURRENT PULMONARY INFECTION

Pressures mm. Hg	*5/24/62*	*20 mos.*	*9/25/62*	*24 mos.*
RA	m 10	a 14	m 3	a 5
RV		70/12		25/6
PA	m 55	68/50	m 14	24/10
LA	m 6		m 10	
Syst. art.	m 65	95/55	m 62	90/50
O_2 Saturation				
LA		80		96
LPV		32		97
Syst. Art.		80		95
Cardiac output l./min./m^2		?		3.9
Pulm. vascular resistance		?		1.0 units/m^2

allow for addition of significant amounts of oxygen by increasing alveolar P_{O_2}.

In those patients with respiratory problems where carbon dioxide retention is significant, and respiratory acidosis is a major factor, assisted ventilation should be instituted to reduce P_{CO_2} and thus also *p*H.

The immediate and rapid administration of alkali is extremely important in these patients, whether the acidosis be due to metabolic or respiratory causes. We have demonstrated that treatment of the acidosis by bicarbonate administration intravenously may result in dramatic improvement even though P_{O_2} cannot be improved.[12]

In summary, this presentation has outlined the profound effects that hypoxemia with the resulting acidosis may have on the circulation and on organs of the body other than the heart, and the peculiar aspects of the fetal and neonatal circulation and the circulation in certain congenital heart lesions, which make these individuals particularly susceptible to these effects.

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